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10. (Amended) The method of claim 1 comprising administering to said individual the complement activation inhibitor prior to the administration of said active ingredient.

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14. (Amended) The method according to claim 1 wherein said amphiphilic carrier is selected from the group consisting of liposomes, colloidal dispersions, particulate biomaterials, radiocontrast agents and emulsifiers.

15. (Amended) The method according to claim 1 wherein said active ingredient is doxorubicin, daunorubicin or amphotericin B.

B4
17. (Amended) The method according to claim 1 wherein active ingredient is hemoglobin or polynucleotide.

REMARKS

Entry of the amendment and reconsideration is respectfully requested. The amendments are in response to points raised in the final Office Action and should lessen the issues on appeal or result in the allowance of the application.

Upon entry of the amendment, claims 1-11, 14, and 16-19 are pending, claims 7-9, 11 and 18-19 remain withdrawn from consideration and claims 1-6, 14, 16 and 17 are before the Examiner.

Claims 1-6, 10, 14, 16 and 17 are amended. Claims 12, 13 and 15 are cancelled. Claim 10 has been reformatted as a dependent claim, depending on claim 1. "A(a)ctive ingredient" is substituted for "drug" throughout the claims and is defined in claim 1. The solvent is clearly indicated to be the pharmaceutical solvent, mentioned in the specification. Other edits to the claims respond to points raised in the Official Action or were undertaken to more clearly present the invention. No new matter is believed to have been introduced.

Rejections under 35 USC 112, Second Paragraph

Claims 1-6, 10 and 12-17 are rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out distinctly claim containing subject matter which applicant regards as his invention.

The claims have been amended to address the points raised in the Official Action which should render the rejection as stated moot. Please note that "particulate biomaterials" is a recognized term of art and that Chemophor® and Chemophor EL® are recognized trademarks. Note attachments A, B, and C.

Withdrawal of the rejection is respectfully requested.

Rejections under 35 USC 103

Claims 1-6, 10 and 12-17 are rejected under 35 USC 103 as being unpatentable over Ko (5,851,528) by itself or in combination with De Lacharrier (5,744,156). Applicant respectfully traverses.

The claims have been amended to more clearly the inventive contribution- the administration of an effective amount of an complement activation inhibitor to reduce the hypersensitivity caused by the presence of a specified active ingredient and/or a specified amphiphilic material.

There is no recognition in either the primary or secondary reference of the specific problem discovered and solved by Applicants.

Ko teaches chimeric molecules composed of a first and second polypeptides, both of which inhibit complement activation. The chimeric proteins are taught to reduce inflammation.

Conditions mentioned include those associated with ischemia-reperfusion, crash injury, burns, ARDS, autoimmune disorders, etc.. Table 1, referred to by the Examiner, lists potential clinical targets of the protein chimeras, i.e. targets to try.¹ None is an immediate complement reaction like that disclosed herein. The Table does mention "Drug Allergy".

"Goodman & Gilman's The Pharmacological Basis of Therapeutics", Ninth Edition, 1996, Chapter 4, "Principles of Toxicology and Treatment of Poisoning" by Curtis D. Klaasen, provides are accepted meanings for "hypersensitivity" and "drug allergy" at pp. 67 and 68 (Attachment D).² The terms hypersensitivity and drug allergy describe the allergic state. There is usually a latency period of at least 1 or 2 weeks. (This contrasts with our specification in that complement activation occurs immediately with no latent period- there is no requirement for induction of antibodies.)

Accordingly, the teaching of Klaasen (Table1) merely suggest potential applications, e.g. "Allergic Reactions" to drugs, which have characteristics that are distinctly different from the immediate complement reactions of the instant invention.

De Lacharriere teaches the use of a substance P antagonist for the preparation of a pharmaceutical composition for treating skin reddening of a neurological origin. There is no

¹ The art of pathological conditions associated with complement activation in the field of complement prior to the instant disclosed invention are described in the attached Table A. Applicants consulted 44 reviews, research, or textbook articles in the field. Many of these reviews, both before and after 1998 (the Ko, et al patent issued on 22 Dec 98), gave comprehensive listing of pathological conditions associated with complement activation. Each of the pathological conditions mentioned by Ko, et al are included. The first mention of immediate non-IgE hypersensitivity reactions mediated by complement was published by Applicants in Feb, 1998.

² Klaasen mentions Type I, II, III and IV reactions. Type I reactions ("anaphylactic") tend to occur quickly after challenge with an antigen to which the individual has been sensitized. These are also termed *immediate hypersensitivity reactions*. These characteristics are similar to the reactions referred to in the instant specification. According to Klaasen, Type I reactions are mediated exclusively by IgE. IgE cannot activate complement. These immediate hypersensitivity reactions are not due to complement. Type II reactions are slow reactions (generally occurring days or weeks later). These reactions are due to the presence of antibodies against tissue antigens. See p. 68, lines 4-5. Type III reactions are also slow reactions, requiring hours, days, or weeks. IgG immune complexes subsequently fix complement and then deposit in tissues to set up a destructive inflammatory responses. These reactions are not rapid anaphylactic reactions. Type IV reactions are mediated by cells, not complement.

mention of hypersensitivity associated with complement activation by amphiphilic molecules nor its treatment in the manner claimed.

The teachings of references, taken alone or in combination, are incomplete and thereby fail to suggest the claimed invention.

Further, it is respectfully submitted that the references fail to suggest their combination.

There is no problem evident in one for which the other is a solution.

Since a *prima facie* case has not been established, withdrawal of the rejection is respectfully requested.

Conclusion

Having addressed all of the rejections and objections, allowance of the application is believed to be in order. A notice to this effect is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 210-380 referencing docket no. WRAIR 97-18 (378332000900). However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,



BY

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

1. (Amended) A method for reducing hypersensitivity side effect [associated with the administration of an] caused by an amphiphilic carrier, and/or active ingredient [containing pharmaceutical composition] comprising administering to a subject a hypersensitivity reducing effective amount of a complement activation inhibitor in conjunction with the active ingredient and the amphiphilic carrier or a pharmaceutical solvent, wherein said amphiphilic carrier is polyethoxylated oil or a derivatized polyethoxylated oil, and wherein the active ingredient is taxol, paclitaxel, Doxil, althesin, cyclosporin, diazepam, didemnin E, echinomycin, propandid, steroids, teniposide, doxorubicin, daunorubicin, amphotericin B, hemoglobin, polynucleotide or multivitamin product [said composition, wherein the complement activation inhibitor is present in an amount to reduce the hypersensitivity effect].
2. (Amended) The method according to claim 1 wherein said composition further comprises [amphiphilic molecule is polyethoxylated oil or a derivative thereof,] emulsifiers or detergent molecules.
3. (Amended) The method according to claim 2 wherein the pharmaceutical solvent is selected from the group of hydrophilic or hydrophobic solvents.
4. (Amended) The method according to claim [3] 1 wherein the polyethoxylated oil [solvent] is [Cremophor or] Cremophor EL.

5. (Amended) The method according to claim 1 wherein said active ingredient [drug] is poorly soluble in water-based solvents and necessitates the addition of emulsifiers to become soluble.

6. (Amended) The method according to claim 2 wherein the active ingredient [pharmaceutical composition includes] is taxol[, althesin, cyclosporin, diazepam, didemnin E, echinomycin, propandid, steroids, teniposide, or multivitamin products].

10. (Amended) [A] The method of claim 1 [for preventing a complement activation reaction in an individual resulting from the administration of a drug composition containing polyethoxilated oil, said method] comprising

administering to said individual [an effective amount of a] the complement activation inhibitor prior to the administration of said active ingredient[drug composition].

14. (Amended) The method according to claim [12] 1 wherein said amphiphilic carrier is selected from the group consisting of liposomes, colloidal dispersions, particulate biomaterials, radiocontrast agents and emulsifiers.

16. (Amended) The method according to claim [15] 1 wherein said [drug] active ingredient is doxorubicin, daunorubicin or amphotericin B.

17. (Amended) The method according to claim [12] 1 wherein the [pharmaceutical composition includes as an active agent] active ingredient is hemoglobin or polynucleotide[s].

TABLE A

Pathologic Conditions Associated with Complement Activation
(Bolded entries were listed in the patent of Ko, et al)

Diseases	References
1. Acute myocardial infarction	(1-4)
2. Adverse drug reactions	<u>none until ours in Feb 1998</u>
3. Alzheimer's Disease	(5-7)
4. Anaphylaxis	(5-7)
5. Asthma	(7)
6. ARDS	(5-7)
7. Arthus reaction	(7, 8)
8. Atheroma	(5, 6)
9. Bowel inflammation	(5, 6)
10. Bullous pemphigoid (bullous diseases)	(7, 9, 10)
11. Behcet's syndrome	(5, 6)
12. Burn injuries	(7)
13. Catheter reactions	(5-7)
14. Cerebral lupus	(5)
15. Crohn's disease	(7, 11)
16. Crush injury(polytrauma)	(12-15)
17. Cryoglobulinemia (i.e., immune complex formation)	(16, 6-8, 16-21)
18. Drug allergy	<u>none until ours in Feb 1998</u>
19. Experimental allergic encephalomyelitis	(7)
20. Experimental allergic neuritis	(7)
21. Forssman shock	(7)
22. Glomerulonephritis	(6, 17, 20, 21)
23. Guillain-Barre syndrome	(5, 6)
24. Goodpasture's disease	(17, 20, 21)
25. Hemolytic anemia (sickle cell anemia)	(7, 17)
26. Hemodialysis	(7)
27. Hemolytic-uremic syndrome	(6)
28. HEMPAS	(5)
29. Hereditary angioedema	(7, 16, 18, 20, 21)
30. Huntington's disease	(7)
31. Hypersensitivity Pneumonitis	(17)
32. Hypovolemic shock	(13, 22-24)
33. Inflammatory (bowel) diseases	(11, 25-29)
34. Infertility	(5, 6)
35. Intestinal ischemia	(11, 30-33)
36. Ischemia/reperfusion injuries	(7)

37. IC-induced vasculitis	(7)
38. ITP	(5, 17)
39. Juvenile rheumatoid	(5, 6)
40. Lupus nephritis	(5, 18)
41. Membranoproliferative glomerulonephritis	(5, 6, 17, 18, 20, 21)
42. Multiple organ failure	(7, 23, 34, 35)
43. Multiple sclerosis	(6, 7)
44. Myasthenia gravis	(5-7, 17, 19)
45. Pancreatitis	(11, 25-29)
46. Paroxysmal Nocturnal Hemoglobinuria	(5, 17, 20, 21)
47. Pemphigus-Pemphigoid	(5, 6)
48. Phototoxic reactions	(5, 6)
49. Pick's disease	(7)
50. Post-bypass (post-pump) syndrome	(5-7, 17)
51. Preeclampsia	(5, 6)
52. Psoriasis	(7)
53. Radiographic contrast media allergy	(36-40)
54. Reperfusion injury	(1-4)
55. Rheumatoid arthritis	(5-8, 16, 17)
56. Rheumatic myocarditis/endocarditis	(17)
57. Septic shock (endotoxinemia)	(7, 8)
58. Serum sickness	(8, 17)
59. Shonlein-Henoch purpura	(17)
60. Sjogren's syndrome	(5, 6)
61. SLE	(16, 6, 7, 16-21)
62. Stroke	(7)
63. Thermal injury (burn and frostbite)	(41-44)
64. Thyroiditis	(5, 6)
65. Transplant rejection (hyperacute allo- and xenograft)	(5, 7, 20, 21)
66. Urticaria	(8)
67. Vascular leak syndrome (IL-2-induced)	(13, 20, 21)
68. Vasculitis	(5, 7, 16, 17, 19)
69. Xenotransplantation	(20, 21)

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Product Name	Technical Literature	Related Information
(R)-(+)-1-Phenyl Ethylamine (R-PEA)	<input type="button" value="technical data sheet"/>	chemicals
(S)-(-)-1-Phenyl Ethylamine (S-PEA)	<input type="button" value="technical data sheet"/>	chemicals
145D	<input type="button" value="technical data sheet"/>	polystyrene
147F	<input type="button" value="technical data sheet"/>	polystyrene
148G	<input type="button" value="technical data sheet"/>	polystyrene
158K	<input type="button" value="technical data sheet"/>	polystyrene
168M	<input type="button" value="technical data sheet"/>	polystyrene
168MO	<input type="button" value="technical data sheet"/>	polystyrene
1-(2-Hydroxyethyl)-2-pyrrolidone	<input type="button" value="technical data sheet"/>	chemicals
Bis-(3-aminopropyl)-polytetrahydrofuran 2100	<input type="button" value="technical data sheet"/>	chemicals
Bis-(3-aminopropyl)-polytetrahydrofuran 750	<input type="button" value="technical data sheet"/>	diols

446C	technical data sheet	polystyrene
467P	technical data sheet	polystyrene
476M	technical data sheet	polystyrene
477I	technical data sheet	polystyrene
486N	technical data sheet	polystyrene
495F	technical data sheet	polystyrene
Accord® herbicide (Canada)	product label	agricultural products
acResin™	technical data sheet	dispersions and paper chemicals
Acronal® - Adhesive Raw Materials	technical data sheet	dispersions and paper chemicals
Acronal® - Architectural Coatings	technical data sheet	dispersions and paper chemicals
Acronal® - Nonwovens / Carpet Binders	technical data sheet	dispersions and paper chemicals
Acronal® - Paper Chemicals - Coating Binders	technical data sheet	dispersions and paper chemicals
Acronal™ Optive	technical data sheet	dispersions and paper chemicals
Acrosol™ - Paper Chemicals	technical data sheet	dispersions and paper chemicals
Acrylic Acid Dimerization	technical data sheet	acrylic monomers
Acrylic Acid Glacial	technical	acrylic

	data sheet	monomers
Adipic Acid Dihydrazine	technical data sheet	specialty intermediates
Afranil® - Paper Chemicals - Process Chemicals	technical data sheet	dispersions and paper chemicals
Alkafoam™ - Paper Chemicals - Coating Additives	technical data sheet	dispersions and paper chemicals
Alkapen™ - Paper Chemicals - Coating Additives	technical data sheet	dispersions and paper chemicals
Alkasan™ - Paper Chemicals - Coating Additives	technical data sheet	dispersions and paper chemicals
Alkasolv™ - Paper Chemicals - Coating Additives	technical data sheet	dispersions and paper chemicals
Alphacryl®	technical data sheet	automotive refinish
N-3Amine N-(2-Aminoethyl)-1,3-propylenediamine	technical data sheet	amines
N-4Amine (N,N'-Bis (3-aminopropyl) ethylenediamine)	technical data sheet	amines
3-Amino-1-propanol	technical data sheet	amines
Aminoethoxyethanol	technical data sheet	amines
Aminoethylethanolamine	technical data sheet	amines
Aminopropylimidazole	technical data sheet	carboxies
Ammonium Bicarbonate	technical data sheet	chemicals
Ammonium Carbamate	technical data sheet	chemicals

Ammonium Carbonate	technical data sheet	chemicals
Ammonium Chloride	technical data sheet	chemicals
Ammonium Sulfate	technical data sheet	chemicals
t-Amyl Alcohol	technical data sheet	specialty intermediates
Aniline	technical data sheet	amines
Anthosin® - Paper Chemicals - Paper Colorants	technical data sheet	dispersions and paper chemicals
Anthranilamide	technical data sheet	carboxies
Anthranilic Acid	technical data sheet	carboxies
Apo-8' Carotenal 20% Dispersion in peanut oil	technical bulletin	human nutrition
Apogee® plant growth regulator	product label	agricultural products
Ascorbic Acid USP	technical bulletin	human nutrition
Avanel® Grades	list of grades and related info	cosmetic ingredients
Avantra® 2710	technical data sheet	polystyrene
Avantra® 525K	technical data sheet	polystyrene
Avantra® 585K	technical data sheet	polystyrene
Avantra® 585K Q402	technical data sheet	polystyrene
Avantra® 595L	technical data sheet	polystyrene

Avantra® 597N	technical data sheet	polystyrene
Avantra® 8130	technical data sheet	polystyrene
Avantra® 8330	technical data sheet	polystyrene
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Product Name	Technical Literature	Related Information
Banvel® herbicide	list of grades and related info	agricultural products
Basagran® herbicide	list of grades and related info	agricultural products
Basamid® Granular soil fumigant (Canada)	product label	agricultural products
Basazol® - Paper Chemicals - Paper Colorants	technical data sheet	dispersions and paper chemicals
Basocoll™ - Paper Chemicals - Coatings Additives	technical data sheet	dispersions and paper chemicals
Basofil® fibers	technical data sheet	industrial fibers
Basonat™ - Adhesive Raw Materials	technical data sheet	dispersions and paper chemicals

Basonat™ - Industrial Coatings	technical data sheet	dispersions and paper chemicals
Basoplast® - Paper Chemicals - Process Chemicals	technical data sheet	dispersions and paper chemicals
Beta Carotene	list of grades and related info	animal nutrition
Beta-Carotene	list of grades and related info	human nutrition
N,N-Bis(3-aminopropyl) methylamine	technical data sheet	amines
Bisabolol	list of grades and related info	cosmetic ingredients
Blazer® herbicide	list of grades and related info	agricultural products
Boron Trifluoride Diethylether Complex	technical data sheet	chemicals
1,4-Butanediol	technical data sheet	diols
Butanediol Monoacrylate	technical data sheet	diols
n-Butanol	technical data sheet	oxo products
2-Butene-1,4-diol	technical data sheet	diols
Butofan® - Adhesive Raw Materials	technical data sheet	dispersions and paper chemicals
Butofan® - Nonwovens / Carpet Backings	technical data sheet	dispersions and paper chemicals
Butonal® - Adhesive Raw Materials	technical data sheet	dispersions and paper chemicals

Butonal® - Asphalt Modifiers	technical data sheet	dispersions and paper chemicals
Butonal® - Nonwovens / Carpet Backings	technical data sheet	dispersions and paper chemicals
Butyl Acrylate	technical data sheet	acrylic monomers
sec-Butylamine	technical data sheet	amines
tert-Butylamine	technical data sheet	amines
Butylamine	technical data sheet	amines
2-Butyne-1,4-diol	technical data sheet	diols
Butyne-1-ol-3 (55%)	technical data sheet	diols
n-Butyraldehyde	technical data sheet	chemicals
gamma-Butyrolactone	technical data sheet	diols
iso-Butyryl Chloride	technical data sheet	carboxies
n-Butyryl Chloride	technical data sheet	carboxies

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Product Name	Technical Literature	Related Information
d-Calcium Pantothenate USP	technical bulletin	human nutrition
Calpan	list of grades and related info	animal nutrition
Calsan™ - Paper Chemicals - Coating	technical data sheet	dispersions and paper

Additives		chemicals
Canthaxanthin	list of grades and related info	animal nutrition
Caprolactone Monomer	technical data sheet	chemicals
Catiofast® - Paper Chemicals - Process Chemicals	technical data sheet	dispersions and paper chemicals
Celebrity® herbicide (USA)	product label	agricultural products
Celebrity™ Plus herbicide	product label	agricultural products
Cetylchloroformate	technical data sheet	carboxies
4'-Chlorobenzophenone-2-carboxylic Acid	technical data sheet	carboxies
4-Chlorobutyrylchloride	technical data sheet	carboxies
2-Chloroethyl Chloroformate	technical data sheet	carboxies
3-Chloropropionylchloride	technical data sheet	carboxies
Citowett® Plus adjuvant (Canada)	product label	agricultural products
Clarity® herbicide (USA)	product label	agricultural products
Conclude® herbicide	list of grades and related info	agricultural products
Cosmetic Colorant Grades	list of grades and related info	cosmetic ingredients
Cosmetic Dyes Grades	list of grades and related info	cosmetic ingredients
Cosmetic Pigments	list of grades	cosmetic

Grades	and related info	ingredients
Cremophor® A Grades	list of grades and related info	cosmetic ingredients
Cremophor® CO Grades	list of grades and related info	cosmetic ingredients
Cremophor® Grades	list of grades and related info	cosmetic ingredients
Cremophor® RH Grades	list of grades and related info	cosmetic ingredients
Curesan™ - Paper Chemicals - Coating Additives	technical data sheet	dispersions and paper chemicals
Cyclohexanol	technical data sheet	amines
Cyclohexanone	technical data sheet	oxo products
Cyclohexene	technical data sheet	chemicals
1,2-Cyclohexene Oxide	technical data sheet	chemicals
Cyclohexylamine	technical data sheet	amines
N-Cyclohexylpyrrolidone	technical data sheet	chemicals
Cyclopentanone	technical data sheet	chemicals
Cycocel® extra plant growth regulator (Canada)	product label	agricultural products

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Product Name	Technical	Related
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	Literature	Information
d-Biotin	list of grades and related info	animal nutrition
Di(2-methoxyethyl)amine	technical data sheet	amines
1,3-Diaminopropane	technical data sheet	amines
Diamont®	technical data sheet	automotive refinish
1,8-Diazabicyclo-5,4,0-undecene-7	technical data sheet	amines
Dibutylamine	technical data sheet	amines
Dicarboxylic Acid Mixture	technical data sheet	specialty intermediates
Diethylhydroxylamine-pure	technical data sheet	chemicals
Diethylhydroxylamine-85%	technical data sheet	chemicals
Diethyl Ketone	technical data sheet	specialty intermediates
Diethylamine	technical data sheet	amines
2-(Diethylamino)ethylamine	technical data sheet	amines
3-(Diethylamino)propylamine	technical data sheet	amines
4-Diethylaminobenzaldehyde	technical data sheet	carboxies
Diethylcarbamoylchloride	technical data sheet	carboxies
Diethylenetriamine	technical data sheet	amines
N,N-Diethylethanolamine	technical data sheet	amines

Dihexylamine	technical data sheet	amines
3,4-Dihydro-2H-pyran	technical data sheet	diols
Dimethoxy-2,5-dihydrofuran	technical data sheet	chemicals
3,3'-Dimethyl-4,4'-diaminodicyclohexylmethane	technical data sheet	amines
Dimethylacetamide	technical data sheet	oxo products
3-(Dimethylamino)propylamine	technical data sheet	amines
4-Dimethylaminobenzaldehyde	technical data sheet	carboxies
N,N-Dimethylaminodiglycol	technical data sheet	amines
N,N-Dimethylbutylamine	technical data sheet	amines
N,N-Dimethylcyclohexylamine	technical data sheet	amines
N,N-Dimethylethanolamine	technical data sheet	amines
Dimethylethylamine	technical data sheet	amines
Dimethylformamide	technical data sheet	oxo products
Dimethylformamide dimethylacetal	technical data sheet	chemicals
1,2-Dimethylimidazole	technical data sheet	carboxies
cis-2,6-Dimethylmorpholine	technical data sheet	amines
Dimethylolurea	technical data sheet	specialty intermediates
1,4-Dimethylpiperazine	technical data sheet	amines

N,N'-Dimethylpiperazine	technical data sheet	amines
N,N'-Dimethylurea	technical data sheet	specialty intermediates
2,2'-Dimorpholinodiethylether	technical data sheet	amines
Dipropylamine	technical data sheet	amines
Dipropylene Glycol	list of grades and related info	cosmetic ingredients
Distinct® herbicide	list of grades and related info	agricultural products
Ditridecylamine	technical data sheet	amines
Dry n-3 Omega 3 fatty acid	list of grades and related info	human nutrition
DyVel® herbicide (Canada)	product label	agricultural products

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Emulsifying agent for the pharmaceuticals, cosmetics and feedstuffs industries; used in aqueous preparations of hydrophobic substances, e.g. fat-soluble vitamins and essential oils.

Common names

Polyoxyethylenglyceroltriricinoleat 35 (DAC), Polyoxy 35 Castor Oil (USP/NF).

Nature

Cremophor EL is a non-ionic solubilizer and emulsifier obtained by causing ethylene oxide to react with castor oil of German Pharmacopoeia (DAB 8) quality in a molar ratio of 35 moles to 1 mole.

Composition

The main component of Cremophor EL is glycerol-polyethylene glycol ricinoleate, which, together with fatty acid esters of polyethyleneglycol, represents the hydrophobic part of the product. The smaller, hydrophilic part consists of polyethylene glycols and ethoxylated glycerol.

Properties

Cremophor EL is a pale yellow, oily liquid that is clear at temperatures above 26 °C. It has a slight but characteristic odour and can be completely liquefied by heating to 26 °C. The hydrophilic-lipophilic balance (HLB) lies between 12 and 14.

Specification

Viscosity (Höppler) at 25 °C	700–850 mPa·s
Mass density at 25 °C	1.05–1.06 g/ml
Refractive index at 25 °C	1.465–1.475
Saponification value	63–72
Hydroxyl value	65–78
Iodine value	28–32
Acid value	≤ 2
Water content (K. Fischer)	≤ 3 %
pH value of 10% aqueous solution	6–8
Sulfated ash	≤ 0.2 %
Heavy metals (USP XX method)	≤ 10 ppm

Unless otherwise indicated, the values were determined according to the monograph "Polyoxyäthylenglyceroltriricinoleat 35" of the Deutscher Arzneimittelcodex and to the monograph "Polyoxy 35 Castor Oil". USP/NF.

Solubility

Cremophor EL forms clear solutions in water. It is also soluble in ethyl alcohol, n-propyl alcohol, isopropyl alcohol, ethyl acetate, chloroform, carbon tetrachloride, trichloroethylene, toluene and xylene.

In contrast to that of anionic emulsifying agents, the solubility in water decreases with rising temperature. Thus, aqueous solutions become turbid at a certain temperature.

Cremophor EL is miscible with all other Cremophor grades and, on heating, with fatty acids, fatty alcohols and certain animal and vegetable oils. It is thus miscible with oleic and stearic acids, dodecyl and octadecyl alcohols, castor oil, and a number of lipid-soluble substances.

Stability

Cremophor EL in aqueous solutions is stable towards electrolytes, e.g. acids and salts, provided that their concentration is not too high. Mercury (II) chloride is an exception and forms a precipitate with the product.

Some organic substances may cause precipitation at certain concentrations, especially compounds containing phenolic hydroxyl groups, e.g. phenol, resorcinol and tannin.

Cremophor EL can be sterilized by heating in an autoclave for 30 minutes at 120 °C. It may thus acquire a deeper shade. During sterilization, Cremophor EL should not be heated together with substances that are strongly acidic or alkaline and would thus saponify it.

Application

Cremophor EL is recommended as a solubilizer and emulsifier in many different branches of industry. It is particularly suitable for the production of liquid preparations.

The degree to which the hydrophobic substance is distributed in the liquid depends largely on its properties and on the amount of Cremophor EL used. A rule of thumb is that, if Cremophor EL is present in excess, clear or opalescent liquids are obtained. However, if the proportion of Cremophor EL is reduced to, say 5–10%, expressed in terms of water-insoluble substance, conditions exist for the formation of an emulsion.

In aqueous solution, Cremophor EL emulsifies or solubilizes the fat-soluble vitamins A, D, E and K. In aqueous-alcoholic solutions, it very readily solubilizes essential oils. Other hydrophobic drugs can also be converted into aqueous solutions with Cremophor EL (e.g. Miconazole, Hexedetine, Clotrimazole, Benzocaine).

In order to ensure that the fat-soluble vitamins yield clear aqueous solutions, they must first be intimately mixed with the solubilizer. The preferred forms of vitamin A for this purpose are vitamin A palmitate with 1.7 million I.U./g or vitamin A propionate with 2.5 million I.U./g; and the preferred form of vitamin K is vitamin K₁ (phytomenadione).

An important factor is how the water-soluble substance is solubilized. Hence, a typical example, viz. the preparation of an aqueous vitamin A palmitate solution with 150000 I.U./ml, is described in detail below.

Vitamin A palmitate 1.7 million I.U./g	8.8 g
Cremophor EL	25.0 g
Water	ad 100 ml

The Cremophor EL is mixed with the vitamin and heated to 60–65 °C. The water, also heated to 60–65 °C, is intimately incorporated in the mixture by slowly stirring in. Initially, thickening occurs as a result of hydration and reaches a maximum when about half of the water has been added. On addition of the remaining water, the viscosity is reduced again. If the first half of the water is added too rapidly, an opalescent solution may be obtained.

The following three diagrams show that clear aqueous solutions of vitamin A palmitate, vitamin A propionate or vitamin E acetate can be obtained in very high concentrations with the aid of Cremophor EL. Concentrations refer to the finished solubilisates.

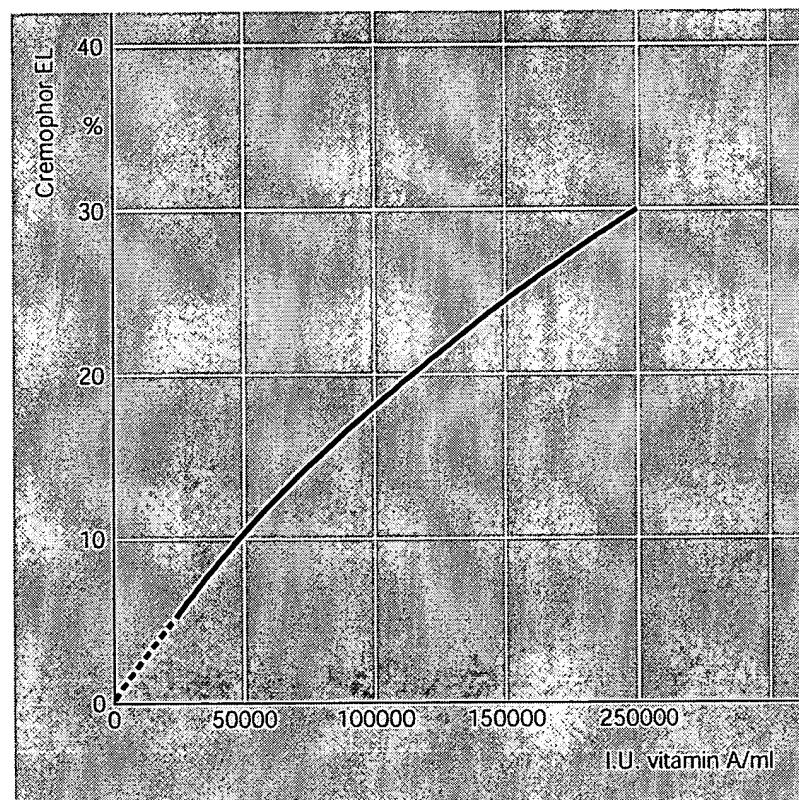


Fig. 1 Vitamin A palmitate

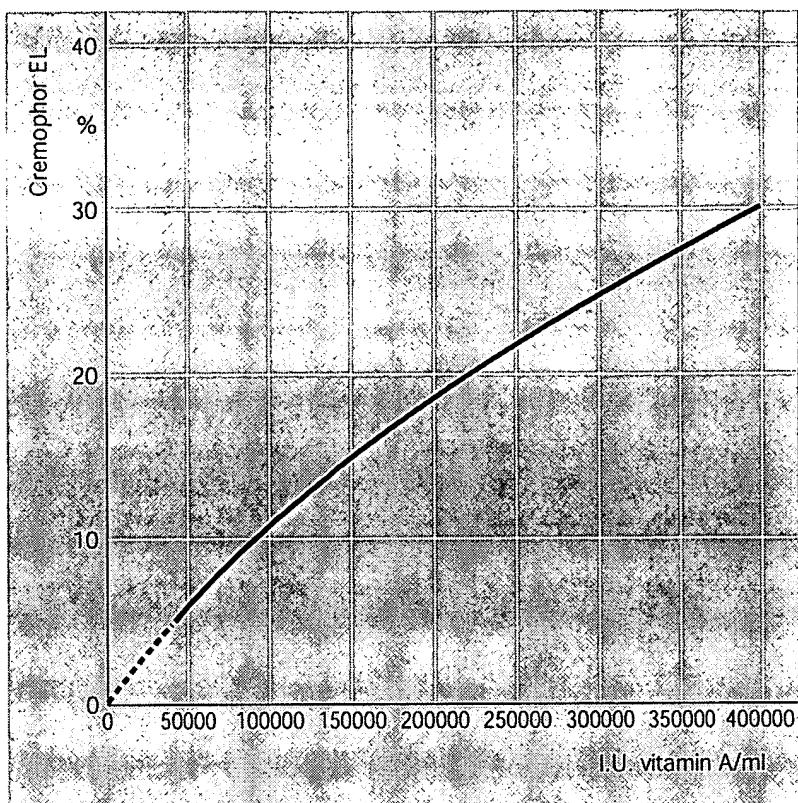


Fig. 2 Vitamin A propionate

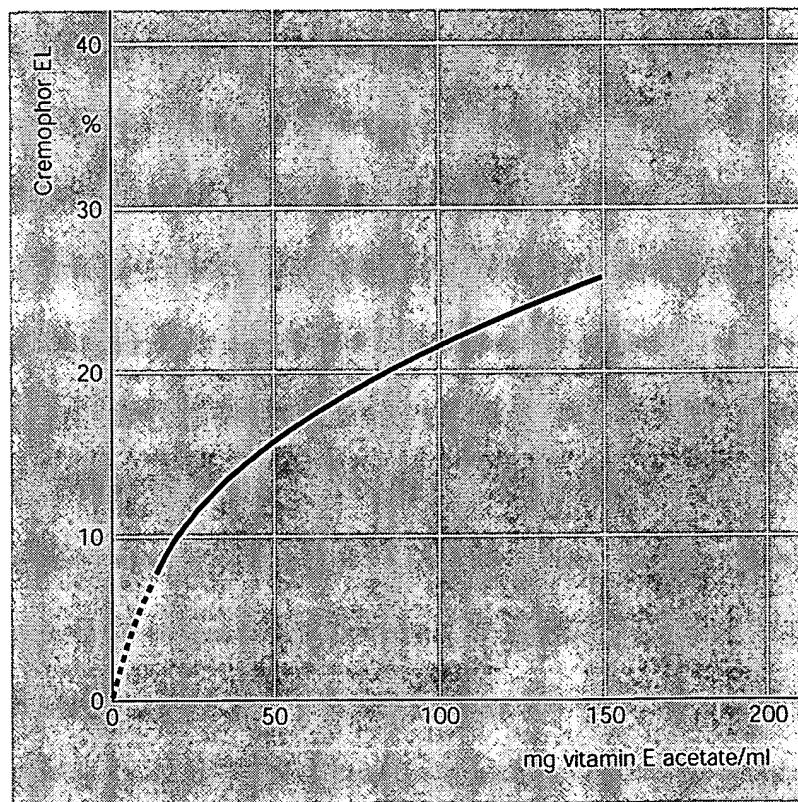


Fig. 3 Vitamin E acetate

The following amounts of other fat-soluble vitamins can be dissolved in a 6% solution of Cremophor EL:

ca. 200000 I.U. vitamin D₃/ml or
ca. 10 mg vitamin K₃/ml

As a rule, less Cremophor EL is required for mixtures of various vitamins.

The processing temperature and, in some cases, the amount of Cremophor EL required can be reduced by adding small amounts of polyethylene glycol (Lutrol® E 400), propylene glycol or glycerol. The stability of many solubilisates may be affected by light.

For reasons of taste, it is recommended that the hydrogenated and thus tasteless form, viz. Cremophor RH 40, be used for oral application in human medicine. The inherent odour of Cremophor EL can best be masked in many cases with banana aroma.

A solution of one part of azulene in about four parts of Cremophor EL can be infinitely diluted with water. In addition, Cremophor EL has proved to be a useful additive in the production of glycerol suppositories.

Cosmetics

In the cosmetics industry, Cremophor EL is used preferentially for solubilizing perfume oils and for emulsifying fatty substances, organic solvents, and additives. Cremophor EL is an outstanding solubilizer for aroma chemicals and ethereal oils in aqueous isopropyl or ethyl alcohol, provided that the alcohol concentration is 30 – 50%. In many cases, extremely small additions of Cremophor EL are adequate under these conditions, so that the inherent odour of the product is completely masked. The solubilizers Cremophor RH 40 and Cremophor RH 60, which are also highly efficient, are completely free from odour and taste.

For the production of completely clear solutions of perfume oil in aqueous alcohol, the perfume oil and the solubilizer should be dissolved together in concentrated alcohol, after which the water is added slowly.

Animal nutrition and veterinary medicine

By virtue of its good dispersing action, Cremophor EL enables nutritive and therapeutic substances to be assimilated more completely and thus renders them more effective. This fact is of particular interest for compounded feeds containing oils and fats. A special application of Cremophor EL is the production of cod-liver oil emulsions in veterinary medicine.

Physiological properties

Acute toxicity

LD 50 (7 days follow-up period):

Rat oral	> 6.4 ml/kg
Rabbit oral	> 10.0 ml/kg
Cat oral	> 10.0 ml/kg
Mouse i.v.	2.5 – 4 ml/kg
Rat percutaneous	> 4.0 ml/kg (maximum applicable dose)

No characteristic toxic symptoms were observed after oral doses or application to the skin, and no pathological changes of the inner organs were discernible with the naked eye during autopsy.

Acute inhalation toxicity

Cremophor EL is practically non-volatile. In tests, rats have inhaled air saturated at 20 °C with the volatile components of the product for over eight hours without suffering any irritation of respiratory tract or any injury by absorption.

Irritation of skin and mucous membranes

Contact for more than 20 hours between the undiluted product and the highly sensitive skin on the backs and ears of white rabbits caused only slight or insignificant inflammation that disappeared rapidly.

This instillation of 0.05 ml of Cremophor EL in the rabbit's conjunctival sac only caused slight reddening of the conjunctiva that disappeared within a few hours. The application of a 50% aqueous solution of the product caused slight irritation and lacrimation, both of which disappeared rapidly; 30% aqueous solutions had no irritant effect.

	Repeated application of a 50% solution of Cremophor EL in acetone with a brush to the skin of guinea-pigs produced inflammatory reactions at the affected parts but did not cause any sensitization. Intracutaneous injection of 0.05 or 0.1 ml of a 0.1% solution in physiological sodium chloride solution ten times on successive days to a guinea-pig did not cause sensitization.
Subacute toxicity	Repeated oral administration of Cremophor EL in doses of 0.5, 1.0, 2.5 and 5.3 ml/kg daily (5 times a week over four weeks) with the oesophageal sound to beagles did not cause any clinically detectable disorder except for soft faeces in some cases. In clinical-chemical and pathological-histological tests, the experimental animals did not show any pathological changes attributable to Cremophor EL.
Feeding tests	In six-month feeding tests carried out on rats and dogs with Cremophor EL in concentrations of up to 1%, the experimental animals showed no visible symptoms of poisoning, no impairment of feed ingestion or growth, no detectable disorders of the blood and urine, no organic malfunctions, no increase in weight of the organs, and no abnormal organic mutation that could be detected in pathological-histological tests (no-effect level).
Teratological effect	No teratological or embryotoxic effect of Cremophor EL (tested according to the FDA specifications: Guidelines for reproduction studies for safety evaluation of drugs for human use; 1966) after oral application of 10 and 5 ml/kg daily from the 6th to the 15th day post coitum with the oesophageal sound was observed in NMRI mice. Even the addition of 10% and 5% of Cremophor EL to the feed of pregnant Sprague-Dawley rats during the organogenesis period, i.e. day 0–20, had no embryotoxic or teratological effect.
Effect on action of drugs	Detailed toxicological test reports on Cremophor EL are available on request.
	The fine degree of dispersion resulting from addition of Cremophor EL allows a drug to be absorbed more readily and increases its efficiency.
	Cremophor EL promotes the penetration of a number of active substances and exerts either activating or inactivating effects on others, e.g. antibiotics. Therefore, before Cremophor EL preparations are used in practice, it is advisable to subject them to thorough pharmacological tests.
	Cremophor EL is subjected to detailed quality control involving comprehensive chemical and physical tests. The individual production batches are not, however, subjected to biological tests. For this reason, all producers of Cremophor EL preparations must carry out their own tests to check the suitability of the material used and the final preparations.
	Cattle that have been subjected to parenteral treatment with certain vaccines or medicaments and subsequently injected with preparations containing Cremophor EL or similar solubilizers have displayed anaphylactoid reactions in isolated, exceptional cases. After the application of injections containing Cremophor EL to human beings, anaphylactoid reactions have sometimes been observed. For this reason, the health authorities in the Federal Republic of Germany and the U.K., for instance, have laid down that the content of polyethoxylated castor oil in injections for parenteral application to human beings must be declared, and any possibility of side effects must be pointed out in the package circular. This is an aspect to which companies producing pharmaceuticals for human beings must pay particular attention.
	After oral administration of preparations containing Cremophor EL, side effects of this kind have not been observed.
Packaging	Drums of 60 kg and 120 kg capacity.
Product number	00647/1/63
Safety Data Sheet	A Safety Data Sheet is available.
Storage	Cremophor EL should be stored in tightly closed containers and protected from light. Prolonged storage is not advisable unless the containers are completely full.

Note

The data submitted in this publication are based on our current knowledge and experience. They do not constitute a guarantee in the legal sense of the term and, in view of the manifold factors that may affect processing and application, do not relieve processors from the responsibility of carrying out their own tests and experiments. Any relevant patent rights and existing legislation and regulations must be observed.

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Attachment

GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

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ILLUSTRATIONS BY EDNA KUNKEL.

biogeochemistry

phology (bi"o-ke-mor-fol'o-je) the study of the relations between chemical constitution and biological action.

-(o-si'dal) pertaining to that which kills living organisms.

-(o-kli-mut'iks) bioclimatology.

logist (bi"o-kli'mah-tol'oh-jist) an individual skilled in biology.

logy (bi"o-kli'mah-tol'oh-je) [bio- + climatology] the study of effects on living organisms of the natural environment (rainfall, daylight, temperature, air movement) prevailing in specific regions. See also biomeclimatology.

subcarbonate of bismuth.

s (bi"o-se-no'sis) biogenesis.

(b'i-o-kol'oid) [bio- + colloid] a colloid from animal, microbial tissue.

ible (bi"o-kom-pat'ih-b'l) being harmonious with life; not toxic or injurious effects on biological function.

ibility (bi"o-kom-pat'ih-bil'it-te) the quality of being able.

ictics (bi"o-ai'ber-net'iks) the science of communication in animals.

i-o-si'k'l [bio- + Gr. kyklas cycle] the rhythmic regular phenomena observed in living organisms.

ible (bi"o-de-grad'ah-b'l) susceptible of degradational processes, as by bacterial or other enzymatic

action (bi"o-deg'rah-dah'shun) the series of processes living systems render chemicals less noxious to the environment.

'o-dos trademark for a preparation of diethylstilbestrol.

s (bi"o-de-tri'tua) detritus derived from the disintegrated decomposition of once-living organisms; further as phytodetritus or zoodetritus, depending on whether the organism was vegetal or animal.

los (bi"o-di-nom'iks) [bio- + Gr. dynamis might] the study of the nature and determinants of all organic human behavior.

ity (bi"o-e'lek-tris'ih-te) the electrical phenomena in living tissues, as that generated by muscle and nerve.

nics (bi"o-e'lek-tron'iks) the study of the role of intertransfer of electrons in biological regulation and control.

l (bi"o-e'l'o-ment) any chemical element that is a part of living tissue.

tica (bi"o-en'er-jet'iks) the study of the energy actions in living organisms.

lence (bi"o-e-kwiv'ah-lens) the quality of being biologically equivalent.

lent (bi"o-e-kwiv'ah-lent) having the same strength or bioavailability in the same dosage form as another of a given drug substance.

lck (bi"o-fed'bak) the process of furnishing an individual, usually in an auditory or visual mode, on the one or more physiological variables such as heart rate, respiration, or skin temperature, such a procedure often is individual to gain some voluntary control over the variable being sampled. **alpha b.**, a procedure in which is presented with continuous information, usually on the state of his brain-wave pattern, with the intent that it will be associated with a state of relaxation and wakefulness. Called also alpha feedback.

oid (bi"o-fla've-noid) a generic term for a group of plants that are widely distributed in plants and that are with maintenance of a normal state of walls of small cells. See flavonoid.

'o-jen [bio- + Gr. gennan to produce] one of several terms supposedly representing the ultimate molecular form.

s (bi"o-jen'ë-sis) [bio- + Gr. genesis origin] 1. the origin of living organisms. 2. the theory that living organisms originate only from other organisms already living.

s (bi"o-jë-net'ik) pertaining to biogenesis.

bi'ojen'ik having origins in biological processes, as in amine.

s (bi"o-jë-nus) originating from life or producing life.

imistry (bi"o-jë'o-kem'ë-trs) [bio- + Gr. gë earth + -mistry] the study of interactions between the biosphere and environment, e.g., the study of the effect of living organisms on the weathering of rocks, of the concentration of by living systems, etc.

biogeography

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biogeography (bi"o-je-o-grah-ik) the scientific study of geographic distribution of living organisms.

biograph (bi"o-uh-graf) 1. an instrument for analyzing and rendering visible the movements of animals; used in diagnosis of certain nervous diseases. 2. spirograph.

biohydraulic (bi"o-hi-draw'lik) [bio- + Gr. hydor water] pertaining to the action of water and solutions in living tissue.

bioimplant (bi"o-im'plant) denoting a prosthesis made of biologically synthetic material.

biokinetics (bi"o-ki-net'iks) [bio- + Gr. kinetikos of or for putting in motion] the science of the movements within developing organisms.

biologic, biological (bi-o-loj'ik; bi-o-loj'ik-al) pertaining to biology.

biologicals (bi-o-loj'ik-alz) medicinal preparations made from living organisms and their products, including serums, vaccines, antigens, antitoxins, etc.

biologist (bi-o-loj'ist) an expert in biology.

biologoe (bi-o-loj'os) [bio- + -logos] the intelligent power displayed in organic activities.

biology (bi-al'oh-je) [bio- + -logie] the science that deals with the phenomena of life and living organisms in general. **molecular b.**, the study of molecular structures and events underlying biological processes, including the relation between genes and the functional characteristics they determine. **radiation b.**, the scientific study of effects of ionizing radiation on living organisms.

bioluminescence (bi"o-loo'mi-nes'ens) chemoluminescence occurring in living cells, especially the emission of light as a result of cellular oxidation of a heat-stable substrate (luciferin) in the presence of a heat-sensitive enzyme (luciferase).

biolysis (bi-o-l'i-sis) chemical decomposition of organic matter by the action of living organisms.

biolytic (bi-o-li'tik) [bio- + Gr. lytikos loosening] 1. pertaining to or characterized by biolysis. 2. destructive to life.

biomass (bi'o-mass) the entire assemblage of living organisms, both animal and vegetable, of a particular region, considered collectively.

biomaterial (bi"o-mah-te're-al) a synthetic dressing with selective barrier properties, used in treatment of burns; it consists of a liquid solvent (polyethylene glycol-400) and a powdered polymer.

biomathematics (bi"o-math'ë-mat'iks) [bio- + mathematics]

mathematics as applied to the phenomena of living things.

biome (bi'om) [Gr. bios life + -ome (-oma) mass] the recognizable community unit of a given region, produced by interaction of climatic factors, biota, and substrate, usually designated according to the characteristic adult or climax vegetation, as tundra, coniferous forest or taiga, deciduous forest, grassland, and the like.

biomechanics (bi"o-me-kan'iks) [bio- + mechanics] the application of mechanical laws to living structures, specifically to the locomotor system of the human body. **dental b.**, the relationship between the biologic behavior of oral structures and the physical influence of a dental restoration.

biomedical (bi"o-med'ikal) biological and medical; pertaining to the application of the natural sciences (biology, biochemistry, biophysics, etc.) to the study of medicine.

biomedicine (bi"o-med'is-in) clinical medicine based on the principles of the natural sciences (biology, biochemistry, biophysics, etc.).

biomembrane (bi"o-mom'brän) any membrane, e.g., cell membrane, of an organism.

biomembranous (bi"o-mem'bräh-nus) of or pertaining to a biomembrane.

biometeorologist (bi"o-me"te-or-ol'o-jist) an individual skilled in biometeorology.

biometeorology (bi"o-me"te-or-ol'o-je) [bio- + Gr. meteors raised from off the ground + logos treatise] that branch of ecology which deals with the effects on living organisms of the extra-organic aspects of the physical environment (such as temperature, humidity, barometric pressure, rate of air flow, and air ionization). It considers not only the natural atmosphere but also artificially created atmospheres such as those to be found in buildings and shelters, and in closed ecological systems, such as satellites and submarines.

biometer (bi-om'ë-ter) [bio- + Gr. metron measure] an apparatus by which extremely minute quantities of carbon dioxide can be measured; used in measuring the carbon dioxide given off from functioning tissue.

biometrician (bi"o-met'rik'yan) an individual skilled in biometry.

biometrics (bi"o-met'riks) biometry.

biometry (bi-om'ë-tre) [bio- + Gr. metron measure] 1. the science of the application of statistical methods to biological facts; mathematical analysis of biological data. 2. in life insurance, the calculation of the expectation of life.

biomicroscope (bi"o-mi'kros'kop) a microscope for examining living tissue in the body. **slit-lamp b.**, Gullstrand's slit lamp.

biomicroscopy (bi"o-mi'kros'kop-ee) the examination of living tissue by a microscope.

biomolecule (bi"o-mö'köl'üf) cell, as a protein.

blomotor (bi"o-mö'kötör) respiratory.

Biomphalaria (b'i-omfah-lä're-ä) species of which is called also Austin's bison (bi'ön) [Gr. 1. gäniām].

bionecrosis (bi"o-nö'kro-sis) force exercised in.

bonergy (bi-on'ë) force exercised in.

bionics (bi-on'iks) the relations of

bionomy (bi-on'ë) edge regarding t

bionosis (bi-o-në) caused by living

bionucleonics (bi-nü-kle'ön-iks) applications of

bio-nostic (bi"o-nö'stik) osmotic pressure

biophagism (bi"o-fä'gizm) living or absorption

biophagous (bi"o-fä'gööüs) biophagy (bi"o-fä'gä-je)

biophore (bi"o-för) the vital un

into groups called

larger ones call

and these in turn

chromosomes. (

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DORLAND'S ILLUSTRATED
Medical
Dictionary

Twenty-sixth Edition

W. B. SAUNDERS COMPANY Philadelphia London Toronto
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bio / bionic

140

bio (bē'ō) *n., pl. bios* [Collins] a biography, often a very brief one — *adj.* [Colloq.] biographical

bio- (bē'ō, -ē) [*Gr. < bios, life < IE base *b^hwei-, to live > Gkē, 1. aware, to live, vita, life. Or biu, living. Or biun, to live, zōion, animal] combining form life, of living things, biological [biography, biochemistry]*

bio-ac-cu-mu-la-tion (bē'ō ak'yoō'myōō lāshōn, -yōō-) *n.* the process in which industrial waste, toxic chemicals, etc. gradually accumulate in living tissue — **bio-ac-cu-mu-late**' (kōō'myōō lātē, -yā-) *vt.*

bio-ac-cu-mu-lat-ive (bē'ō ak'yoō'myōō lātīv, -lat iv, -yā-) *adj.*

bio-a-cous-tics (-ō kōō'stiks) *n.pl.* [with sing. *v.*] a branch of acoustics that deals with sounds produced and perceived, esp. for communication, by animals

bio-ac-tive (-ākt'iv) *adj.* having a capacity to interact with a living tissue or system — **bio-ac-tiv-ity** (-ākt'iv'ētē) *n.*

bio-as-say (bē'ō as'sā) *n.* [Mod. + -say] a technique for determining the power of a drug or other substance by measuring its effects on a test specimen against those of a standard substance

bio-as-tron-au-tics (bē'ō ăstrō nōōtiks) *n.pl.* [with sing. *v.*] the science that deals with the physical responses of living things in the environment of space and space travel

bio-a-vail-a-bil-ity (-ō vāl'ē bē'ētē) *n.* the rate at which a drug, trace element, etc. enters the bloodstream and is circulated to specific organs or tissues

bio-acti-vate (bē'ō akt'iv ītē) *n.* a substance, as an enzyme or hormone, that activates or speeds up a biochemical reaction — **bio-acti-vat-ive** (-ākt'iv ītē) *adj.*

bio-coen-o-sis (bē'ō sēnōō sēs) *n.* [Mod. < Gr. koīnōōs, a mingling < koīnōō, to share < koīnos, common see COENO-] a community of biologically integrated and interdependent plants and animals. Also **bio-coe-nosis** (-ō nōōs) or **bio-e-co-nose** (-ōē nōōs)

biochemical oxygen demand 1 the amount of dissolved oxygen needed to decompose the organic matter in waste water; a high BOD indicates heavy pollution with little oxygen remaining for fish 2 the organic matter in waste water Also **biological oxygen demand**

bio-chem-i-stry (-kēm'ē trē) *n.* a science that deals with the chemistry of life processes in plants and animals — **bio-chem-i-stic** *adj.*, *n.* — **bio-chem-i-st** *n.*

bio-cide (bē'ō sīd') *n.* [Mod. + -cide] a poisonous chemical substance that can kill living organisms, esp. microorganisms

bio-clean (bē'ō klēn') *adj.* as completely free as possible from microorganisms, esp. so as to be aseptic

bio-clim-a-to-logy (bē'ō klim'ōō tōl'ōōjē) *n.* the science that deals with the effects of climate on living matter — **bio-clim-a-tic** (-tik) *adj.*

bio-com-pat-i-ble (-kōō pāt'ē bēl) *adj.* compatible with living tissue, as a prosthetic material or device that is not rejected or does not cause infection — **bio-com-pat-i-bil-ity** *n.*

bio-con-ver-sion (-kōō vār'shōōn, -shōōn) *n.* a process in which a fuel is generated from waste matter, plant matter, etc. as in using bacteria to feed on waste to produce methane

bio-cy-ber-net-ics (-ēbēr net'iks) *n.pl.* [with sing. *v.*] the branch of cybernetics that deals with the control and communication systems of living organisms — **bio-cy-ber-net-ic** *adj.*

bio-degrad-a-ble (-di grād'ē bēl) *adj.* [bio- + DEGRAD- (ē) -ABLE] capable of being readily decomposed by microbial action, as some detergents — **bio-degrad-a-bil-ity** or **bio-degrad-a-tion** (-dgrād'ē shōōn) *n.* — **bio-degrade** *vt.*

bio-eco-logy (-ēkōō lōōjē) *n.* [Mod. + ECOLOGY] the science that deals with the interrelations of communities of animals and plants with their environment

bio-elec-tric (-ē lēk'ē trēk) *adj.* or *of* having to do with electrical energy in living tissues Also **bio-elec-trical** — **bio-elec-tric-i-ty** *n.*

bio-elec-tron-ics (-ēlek' trōōn'iks, -ēlek') *n.pl.* [with sing. *v.*] a branch of electronics that deals with electronic devices, implants, etc. used in medicine and biological research — **bio-elec-tron-ic** *adj.*, **bio-elec-tron-i-cally** *adv.*

bio-en-er-get-ics (-ēn'ēr jēt'iks) *n.pl.* [with sing. *v.*] a branch of energetics that deals with how a living organism converts food, sunlight, etc. into useful energy — **bio-en-erget-ic** *adj.*

bio-en-gi-neer-ing (-ēn'ēj nēr'ēng) *n.* a science dealing with the application of engineering science and technology to problems of biology and medicine — **bio-en-gi-neer** *n.*

bio-equival-ence (-ē kwī'ē lēns, -ē) *n.* the equality of strength, bioavailability, and dosage of various drug products Also **bio-equiva-lent-cy**, **bio-equivalent** *adj.*

bio-eth-ics (-ēth'iks) *n.pl.* [with sing. *v.*] the study of the ethical problems arising from scientific advances, esp. in biology and medicine — **bio-eth-i-cal** *adj.*

bio-feed-back (-fēd'bāk') *n.* a technique of seeking to control certain emotional states, such as anxiety or depression, by training oneself with the aid of electronic devices, to modify autonomic body functions, such as blood pressure or heartbeat

bio-fla-von-oid (-flā'vōō nōōid, -flā'vōō-) *n.* any of a group of biologically active flavone compounds that may help maintain the blood's capillary walls, reducing the likelihood of hemorrhaging, widely found in plants, esp. citrus fruits

bio-graph 1 biographer 2 biographical 3 biography

bio-gas (bē'ō gās') *n.* a fuel gas produced by fermenting organic waste, as in capturing methane from manure

bio-gen-e-sis (bē'ō jēn'ē sis) *n.* [Mod. + -genesis] 1 the principle that living organisms originate only from other living organisms closely similar to themselves 2 the generation of organisms in this way — **bio-gen-e-tic** (-jēn'ētik) or **bio-gen-e-tical** *adj.* — **bio-gen-e-ti-cally** *adv.*

bio-gen-ic (bē'ō jēn'ēk) *adj.* produced by, or essential to, living cells

bio-geo-chem-i-cal cycle (bē'ō jēō' kēm'ē kāl) the cyclic in which nitrogen, carbon, and other inorganic elements of the soil, atmospheric, etc. of a region are converted into the organic substances of animals or plants of the region and released back into the environment

bio-geog-ra-phy (bē'ō jēō' grāfē) *n.* the branch of biology that deals with the geographical distribution of plants and animals — **bio-geog-ra-phi-c** (-ē grāf'ik) *adj.*

bi-og-ra-phi-ee (bē'ō grāfē īfē, -fēōō bē'ē) *n.* a subject of a biography

bi-og-ra-phier (bē'ō grāfē īfē, -fēōō bē'ē) *n.* a writer of a biography or biographies

biog-ra-phi-cal (bē'ō grāfē kāl) *adj.* 1 of, having to do with, or characteristic of biography or biographies 2 giving the story of, or based on, a person's life Also **biograph-ic** — **biograph-i-cally** *adv.*

biog-ra-phy (bē'ō grāfē) *n.* [Mod. & -GRAPHY] 1 the histories of individual lives, considered as a branch of literature 2 *pl.* — *phēōō* an account of a person's life, described by another, life story

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VICTORIA NEUFELDT

Editor in Chief

DAVID B. GURALNIK

Editor in Chief Emeritus



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*Dedicated
to David B. Guralnik
lexicographical mentor
and friend*

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CHAPTER 4 PRINCIPLES OF TOXICOLOGY AND TREATMENT OF POISONING

brain. Next in order of frequency of involvement in systemic toxicity are the circulatory system; the blood and hematopoietic system; visceral organs such as liver, kidney, and lung; and the skin. Muscle and bone are least often affected. With substances that have a predominantly local effect, the frequency of tissue reaction depends largely on the portal of entry (skin, gastrointestinal tract, or respiratory tract). **Reversible and Irreversible Toxic Effects.** The effects of drugs on human beings must, whenever possible, be reversible; otherwise the drugs would be prohibitively toxic. If a chemical produces injury to a tissue, the capacity of the tissue to regenerate or recover will largely determine the reversibility of the effect. Injuries to a tissue such as liver, which has a high capacity to regenerate, usually are reversible; injury to the CNS is largely irreversible, because the highly differentiated neurons of the brain cannot divide and regenerate.

Delayed Toxicity. Most toxic effects of drugs occur at a predictable (usually short) time after administration. However, such is not always the case. For example, aplastic anemia caused by chloramphenicol may appear weeks after the drug has been discontinued. Carcinogenic effects of chemicals usually have a long latency period, and 20 to 30 years may pass before tumors are observed. Because such delayed effects cannot be assessed during any reasonable period of initial evaluation of a chemical, there is an urgent need for reliable predictive, short-term tests for such toxicity as well as for systematic surveillance of the long-term effects of marketed drugs and other chemicals (see Chapter 3).

Chemical Carcinogens. Chemical carcinogens are classified into two major groups, *genotoxic* and *non-genotoxic* carcinogens. Genotoxic carcinogens interact with DNA, whereas nongenotoxic carcinogens do not. Chemical carcinogenesis is a multistep process. Most genotoxic carcinogens are themselves unreactive (*procarcinogens* or *proximate carcinogens*) but are converted to *primary* or *ultimate carcinogens* in the body. The cytochrome P450-dependent monooxygenases of the endoplasmic reticulum often convert the proximate carcinogens to reactive electron-deficient intermediates (electrophiles). These reactive intermediates can interact with electron-rich (nucleophilic) centers in DNA to produce a mutation. Such interaction of the ultimate carcinogen with DNA in a cell is thought to be the initial step in chemical carcinogenesis. The DNA may revert to normal if DNA repair mechanisms operate successfully; if not, the transformed cell may grow into a tumor that becomes apparent clinically.

Nongenotoxic carcinogens, also referred to as *promoters*, do not produce tumors alone but potentiate the effects of genotoxic carcinogens. Promotion involves facilitation of the growth and development of so-called dormant or latent tumor cells. The time from initiation to the development of a tumor probably depends on the presence of such promoters; for many human tumors the latent period is 15 to 45 years.

To determine whether or not a chemical is potentially carcinogenic to humans, two main types of laboratory tests

of study is performed to determine

whether or not the chemical is mutagenic, because many carcinogens are also mutagens. These studies are often *in vitro* studies, such as the Ames test using *Salmonella typhimurium* (Ames *et al.*, 1975), which can be completed within a few days. This type of test can detect genotoxic carcinogens but not promoters. The second type of study to detect chemical carcinogens consists of feeding laboratory animals (mice and rats) the chemical at high dosages for their entire life span. Autopsies and histopathological examinations are performed on each animal. The incidence of tumors in control animals and animals fed the chemical are compared to determine whether the chemical produces an increased incidence of tumors. This latter study can detect promoters as well as genotoxic carcinogens.

Allergic Reactions. *Chemical allergy* is an adverse reaction that results from previous sensitization to a particular chemical or to one that is structurally similar. Such reactions are mediated by the immune system. The terms *hypersensitivity* and *drug allergy* often are used to describe the allergic state.

For a low-molecular-weight chemical to cause an allergic reaction, it or its metabolic product usually acts as a hapten, combining with an endogenous protein to form an antigenic complex. Such antigens induce the synthesis of antibodies, usually after a latent period of at least 1 or 2 weeks. Subsequent exposure of the organism to the chemical results in an antigen-antibody interaction that provokes the typical manifestations of allergy. Dose-response relationships usually are not apparent for the provocation of allergic reactions.

Allergic responses have been divided into four general categories, based on the mechanism of immunological involvement (Coombs and Gell, 1975). Type I, or anaphylactic, reactions in human beings are mediated by IgE antibodies. The Fc portion of IgE can bind to receptors on mast cells and basophils. If the Fab portion of the antibody molecule then binds antigen, various mediators (histamine, leukotrienes, prostaglandins) are released and cause vasodilation, edema, and an inflammatory response. The main targets of this type of reaction are the gastrointestinal tract (food allergies), the skin (urticaria and atopic dermatitis), the respiratory system (rhinitis and asthma), and the vasculature (anaphylactic shock). These responses tend to occur quickly after challenge with an antigen to which the individual has been sensitized and are termed *immediate hypersensitivity reactions*.

Type II, or cytolytic, reactions are mediated by both IgG and IgM antibodies and usually are attributed to their ability to activate the complement system. The major target tissues for cytolytic reactions are the cells in the circulatory system. Examples of type II allergic responses include penicillin-induced hemolytic anemia, methyldopa-induced autoimmune hemolytic anemia, quinidine-induced thrombocytopenic purpura, sulfonamide-induced granulocytopenia, and hydralazine- or procainamide-induced systemic lupus erythematosus. Fortunately, these autoimmune reactions to drugs usually subside within several months after removal of the offending agent.

Type III, or Arthus, reactions are mediated predominantly by IgG; the mechanism involves the generation of antigen-antibody

SECTION I GENERAL PRINCIPLES

complexes that subsequently fix complement. The complexes are deposited in the vascular endothelium, where a destructive inflammatory response called *serum sickness* occurs. This phenomenon contrasts with the type II reaction, in which the inflammatory response is induced by antibodies directed against tissue antigens. The clinical symptoms of serum sickness include urticarial skin eruptions, arthralgia or arthritis, lymphadenopathy, and fever. These reactions usually last for 6 to 12 days and then subside after the offending agent is eliminated. Several drugs, such as sulfonamides, penicillins, certain anticonvulsants, and iodides, can induce serum sickness. Stevens-Johnson syndrome, such as that caused by sulfonamides, is a more severe form of immune vasculitis. Symptoms of this reaction include erythema multiforme, arthritis, nephritis, CNS abnormalities, and myocardiitis.

Type IV, or delayed-hypersensitivity, reactions are mediated by sensitized T lymphocytes and macrophages. When sensitized cells come in contact with antigen, an inflammatory reaction is generated by the production of lymphokines and the subsequent influx of neutrophils and macrophages. An example of type IV or delayed hypersensitivity is the contact dermatitis caused by poison ivy.

Idiosyncratic Reactions. *Idiosyncrasy* is defined as a genetically determined abnormal reactivity to a chemical. The observed response is qualitatively similar in all individuals, but the idiosyncratic response may take the form of extreme sensitivity to low doses or extreme insensitivity to high doses of the agent. For example, many black males (about 10%) develop a serious hemolytic anemia when they receive primaquine. Such individuals have a deficiency of erythrocytic glucose-6-phosphate dehydrogenase (see Chapter 40). Genetically determined resistance to the anticoagulant action of warfarin is due to an alteration in the vitamin K epoxide reductase (see Chapter 54).

Interactions between Chemicals. The existence of numerous toxicants requires consideration of their potential interactions (see Figure 4-6). Concurrent exposures may alter the pharmacokinetics of drugs by changing rates of absorption, the degree of protein binding, or the rates of biotransformation or excretion of one or both interacting compounds. The pharmacodynamics of chemicals can be altered by competition at the receptor; for example, atropine is used to treat organophosphate insecticide toxicity, because it blocks muscarinic cholinergic receptors and prevents their stimulation by excess acetylcholine resulting from inhibition of acetylcholinesterase by the insecticide. Nonreceptor pharmacodynamic drug interactions also can occur when two drugs have different mechanisms of action; for example, aspirin and heparin when given together can cause unexpected bleeding. The response to combined toxicants may thus be equal to, greater than, or less than the sum of the effects of the individual agents.

Numerous terms describe pharmacological and toxicological interactions (see Figure 4-6, B). An *additive effect* describes the combined effect of two chemicals that is equal to the sum of the effect of each agent given alone; the additive effect is the most common. A *synergistic effect* is one in which the combined effect of two chemicals is greater than the sum of the effect of each agent given alone. For example, both carbon tetrachloride and ethanol are hepatotoxins, but together they produce much more injury to the liver than expected from the mathematical sum of their individual effects. *Potentiation* is the increased effect of a toxic agent acting simultaneously with a nontoxic one. Isopropanol alone, for example, is not hepatotoxic; however, it greatly increases the hepatotoxicity of carbon tetrachloride. *Antagonism* is the interference of one chemical with the action of another. An antagonistic agent is often desirable as an antidote. *Functional or physiological antagonism* occurs when two chemicals produce opposite effects on the same physiological function. For example, this principle is applied to the ability of an intravenous infusion of dopamine to maintain perfusion of vital organs during certain severe intoxications characterized by marked hypotension. *Chemical antagonism or inactivation* is a reaction between two chemicals to neutralize their effects. For example, dimercaprol (BAL) chelates with various metals to decrease their toxicity (see Chapter 66). *Dispositional antagonism* is the alteration of the disposition of a substance (its absorption, biotransformation, distribution, or excretion) so that less of the agent reaches the target organ or its persistence there is reduced (see below). *Antagonism at the receptor* for the chemical entails the blockade of the effect of an agonist with an appropriate antagonist that competes for the same site. For example, the antagonist, naloxone, is used to treat respiratory depression produced by opioids (see Chapter 23).

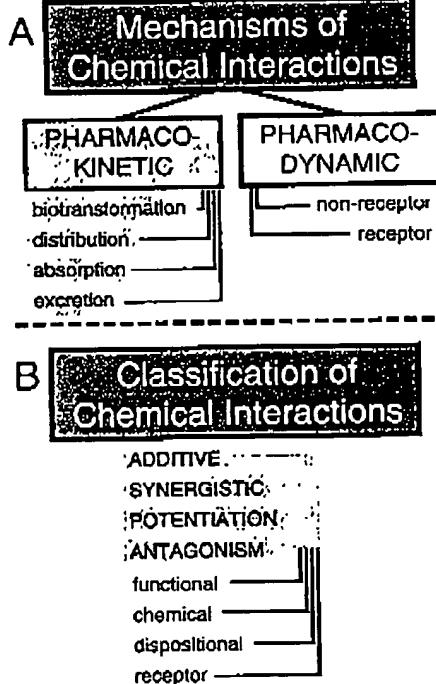


Figure 4-6. Mechanisms and classifications of chemical interactions.